

§ 707.07(f) maintains that when Applicants traverse any rejection, the Examiner should note and rebutt the substance of Applicants' arguments if repeating the rejection. Section 707.07(g) further states that where a rebuttal is applicable it should be stated with a full development of reasons. Mere conclusions coupled with stereotyped expressions represent undesirable, piecemeal examinations, which should be avoided.

Considering the present final Office Action and the Office Action mailed April 16, 2001, the § 103(a) rejection in the final Action is repeated in nearly identical fashion. Significantly, however, the final Action does not address Applicants' § 103 arguments with respect to, for example, the deficiencies of the references and the lack of motivation or suggestion to combine the references. Rather, the Examiner summarily states: "Since the arguments presented in the Response filed by Applicant on 7/21/2001 are obviated by this Office Action, they are not specifically addressed." (Office Action, page 11). Thus, by repeating the § 103 rejection in the final Action, but not addressing the substance of Applicants' previously raised § 103 arguments, there is no foundation on which Applicants may readily assess the advisability of an appeal — no clear issue has been developed between the Examiner and Applicants.

Moreover, Applicants' analysis comports with binding precedent, which requires administrative agencies and personnel to make of record the rationale on which it relies. (See generally, *In re Sang-Su Lee*, 277 F.3d 1338 (Fed. Cir. 2002)). Thus, Applicants consider this final Action to be issued in haste.

This latter statement is further evidenced when considering that claims 27, 30, 32-35, 38-44, 47, 50-52, and 54 in the final Action are not described in light of the amendments made in Applicants' previous reply. (Compare final Action, pages 2-4 with first Action, mailed April 16, 2001, pages 4-5). Additionally, although the Examiner cites Okayama on page 7 of the present Action, that reference does not form the basis for the Examiner's rejection on page 2.

For the above reasons, reconsideration and withdrawal of the finality of the present Office Action is respectfully requested under MPEP § 706.07 (d).

Notwithstanding the above analysis, Applicants will attempt to address the issues in the present final Action. The claims are rejected under 35 U.S.C. § 103(a). Each rejection will be addressed individually below.

Rejection under 35 U.S.C. §103(a)

Claims 27-42 and 47-57 are rejected as obvious over Kamb et al., U.S. Patent No. 6,020,240 ("Kamb"). The rejection is traversed for the following reasons.

Applicants reassert their argument that the Examiner has not established a *prima facie* case of obviousness. Applicants note that the claimed invention recites a method that includes two fractionation steps: one fractionation step carried out on the population of nucleic acid molecules to provide the set of nucleic acid molecules (step (b)), and an additional fractionation step carried out on the recovered nucleic acids to provide the recovered subset (step (f)).

The combination of Kamb and Okayama, when considered as a whole, fails to suggest the desirability of the claimed invention. Applicants noted previously that there are several deficiencies in relying on Kamb as a reference. First, Kamb, when considered as a whole, addresses a different problem from that of the present invention, which is identifying a nucleic acid sequence. Specifically, Kamb relates to a method for the comparative assessment of the level of specific nucleic acid sequences in samples derived from different sources (see Abstract and col. 5, lines 55-62). According to tenet (B) articulated in MPEP § 2141, the Examiner may not consider a portion, such as columns 26-27 (see Office Action, pages 6), without relating the disclosure to the reference as a whole. Applicants submit that an art worker seeking to identify a nucleic acid sequence would not have turned to a reference, such as Kamb, that addresses a different problem, namely that of the comparative assessment of the level of specific nucleic acid sequences in samples derived from different sources. Thus, Kamb is nonanalogous art, and as such is an improper bar under § 103.

Further to the statement that Kamb is nonanalogous art, Kamb teaches the use of at least two independent cell types for vector formation rather than the single vector claimed in the instant application. (*Compare* Kamb, col. 30, ll. 13-38 *with* instant claim 47). Rather than urging the use of Representational Difference Analysis ("RDA"), as implied by the Examiner, Kamb teaches away from this process as one beset with difficulties. (*See* Kamb, col. 27, ll. 28-31).

Moreover, Kamb does not teach two fractionation steps such as required in either claim 27 or claim 56. At most, Kamb discloses only a single step that separates nucleic acids from one

another, namely, the preparation of gene libraries in vectors or plasmids that are propagated in cells, and screening them according to procedures such as biochemical screens or genetic screens (col. 26, line 49-col. 27, line 21). By not disclosing two fractionation steps, Kamb does not provide elements of the presently claimed method of identifying a nucleic acid. Accordingly, Kamb cannot be properly used as part of the obviousness rejection.

— Additionally, there is no support provided for the assertion in the present Office Action that it would have been obvious “to one of ordinary skill” in the art . . . to fractionate both the set and the subset of nucleic acid, due to the beneficial effects. (Office Action, page 6). If it was so obvious, the Examiner should provide an appropriate art reference that predates Applicants’ filing date. To the contrary, if the invention were in fact obvious, because of its advantages, those skilled in the art would have implemented it by now. The fact that no appropriate art references were cited that implement this aspect of the present invention, despite its numerous advantages (specification, page 4), militates in favor of patentability. Moreover, as stated above, such conclusory statements regarding the present state of the art are not permitted, in the context of an obviousness determination, when dealing with particular combinations of prior art and specific claims. (See *In re Sang-Su Lee*, 277 F.3d 1338, 1345 (Fed. Cir. 2001)). Rather, the Examiner must set forth the rationale on which she relies. (See *id.*).

Furthermore, according to MPEP § 2141, the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention. By isolating the disclosure of cols. 26-27 of Kamb, the Office Action appears to have engaged precisely in just such impermissible hindsight.

In summary, Kamb fails as a reference against the present invention because a) it does not disclose two fractionation steps, b) an artisan would not have turned to Kamb in order to solve the problem of identifying a nucleic acid sequence, and c) applying Kamb represents impermissible hindsight reconstruction. Reconsideration and withdrawal of this rejection is respectfully requested.

Due to the Examiner’s citation of Okayama on page 7 of the present Action, Applicants presume that the Examiner intended to reiterate the previous rejection of claims 27-42 and 47-57 as obvious in view of Kamb and further in view of Okayama, Mol. Cel. Biol., 2:161-70

("Okayama"). (See Office Action, mailed April 16, 2001, p. 4). The presumed basis for this rejection is traversed for the following reasons.

The deficiencies of Kamb, detailed above, are not overcome by Okayama. Okayama similarly does not disclose a method comprising the sequence of steps recited in claim 27, including the two fractionation steps. Okayama teaches the use of electrophoresis to separate nucleotides of various sizes and subsequent DNA sequencing, but unlike the instant application, Okayama also teaches that no nucleases are used in its process. (See Okayama, Abstract). This is a significant difference from the instant application wherein restriction endonucleases are utilized. Thus, even if properly combined, these references would not meet the claims of the present invention.

Finally, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings (MPEP Section 2143). The Office Action cites Okayama on page 7, 2nd paragraph, without offering any basis for modifying Kamb, or for combining their teachings. Kamb neither teaches nor suggests the beneficiality of fractionating and recovering a first sample from, *e.g.*, a genomic pool to allow for the separation of a specific gene or chromosome, nor, *e.g.*, the creation of a library from this population with subsequent fractionation of the population, recovery, isolation, and sequencing of the subset. Thus, Kamb lacks the necessary motivation for a case of obviousness under *Graham v. John Deere*. Therefore, the *prima facie* case of obviousness based on Kamb in view of Okayama fails. Moreover, each reference is complete and functional in itself. Thus, there would be no reason, or motivation, to use parts from or add or substitute parts to either reference.

Additional limitations presented in the claims depending from claims 27 and 56 further render the claimed invention non-obvious in view of the cited references. Applicants note that claims specifying length differences (claims 38-42), pooling (claim 50), a replaceable matrix formulation (claim 53) and multiplexing (claim 57) are not disclosed or suggested in any way in the cited references. These dependent claims are therefore clearly not obvious over the cited Kamb and Okayama.

In view of the foregoing comments, reconsideration and withdrawal is respectfully requested of the rejection for obviousness over the presumed combination of Kamb and Okayama.

Claims 43-46 are rejected as obvious over the combination of Kamb, Okayama, and further in view of Macevicz et al., US Patent No. 6,136,537 ("Macevicz"). The rejection is traversed for the following reasons.

Claims 43-46 depend from claim 27. Applicants have demonstrated above that claim 27 is nonobvious over Kamb in view of Okayama. Macevicz fails to supply those elements lacking in Kamb and Okayama. Therefore not all the features of claims 43-46, including those recited in the base claim, claim 27, are found in the combination of references. Claims 43-46 are therefore nonobvious over the combination of Kamb, Okayama, and Macevicz.

Similar to Kamb, Macevicz, considered as a whole, addresses a different problem from that of identifying a nucleic acid sequence. Specifically, Macevicz relates to a method for analyzing the frequency of sequences in a population of polynucleotides. Restriction fragments are ligated together to form a pair of segments that serves as a tag for the restriction fragment (see Abstract). According to tenet (B) of MPEP § 2141, the Examiner may not consider a portion of a reference, such as col. 2 of Macevicz (see Office Action, pages 10-11), without relating the disclosure to the reference as a whole.

Applicants respectfully submit that Macevicz is nonanalogous art, and thus is an improper bar under § 103. Macevicz teaches a process step for re-circularizing an insertion-vector; a step that is lacking in the instant process (See Macevicz, col. 2, ll. 38-67). Conversely, the instant process teaches a PCR-type amplification step that is lacking in Macevicz. Moreover, Macevicz teaches ligating segments from restriction fragments to form a pair of segments that provide a restriction fragment tag. (Compare Macevicz, col.19, claim 1, ll. 35-58, and especially ll. 44-53 with instant specification, pg. 11, ll. 9-18). Thus, Macevicz does not provide the necessary motivation for the instant process taken as a whole. As such, an art worker seeking to identify a nucleic acid sequence would not have turned to Macevicz, which addresses analyzing the overall frequency of sequences in a population of polynucleotides.

Furthermore, according to MPEP § 2141, the references must be viewed without the benefit of impermissible hindsight vision afforded by the claimed invention. By isolating the disclosure of col. 2 of Macevicz, the Office Action appears to have engaged precisely in just such impermissible hindsight. (See MPEP § 2141, citing *Hodosh v. Block Drug Co.*, 786 F.2d 1136, 1143 & n.5 (Fed. Cir. 1986)).

Finally, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings (MPEP § 2143). The Office Action cites Macevicz on page 11, 2nd paragraph, without offering any basis for modifying Kamb and Okayama, or for combining their teachings with those of Macevicz. Although the Examiner is permitted to draw upon her own background and information to reject claims, the Examiner must substantiate that rejection with an underlying rationale. (*See In re Sang-Su Lee*, 277 F.3d 1338, at 1345). However, no rationale was given. Therefore, the *prima facie* case of obviousness based on Kamb in view of Okayama, and further in view of Macevicz, fails.

In view of the foregoing comments, reconsideration and withdrawal of the rejection is requested.

CONCLUSION

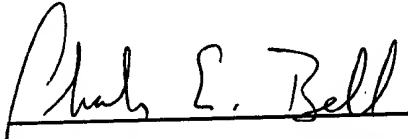
Applicants submit that the application is in condition for allowance and such action is respectfully requested.

Should any questions or issues arise concerning the application, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

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U.S.S.N. 09/614,505

A Notice of Appeal and Petition for Extension of Time accompany this paper. The Commissioner is hereby authorized to charge payment of any additional filing fees required in connection with the papers transmitted herewith, or credit any overpayment of same, to Deposit Account No. 50-0311, Reference No. 15966-539 CIP (Cura-39 CIP).

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